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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,181	SCHEFFER ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 11/12/2009.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Withdrawn Objection to the Specification – Sequence Compliance

1. The objection to the specification for failure to comply with the sequence rules, as set forth on pages 2-3 of the Office Action of 06/10/2009, is **WITHDRAWN** in light of the amendments to the specification of 11/12/2009, which are entered.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

2. The rejections of claims under 35 U.S.C. 112, second paragraph, as being indefinite, as set forth on pages 3-4 of the Office Action of 06/10/2009, are **WITHDRAWN** in light of the amendments to the claims.

Maintained Claim Rejections - 35 USC § 103

3. Claims 1-10, 17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heron et al (2002) (citation #6 on the IDS of 5-25-2006).

Heron et al teaches several phenotypic parameters of BFIS, BFNS, and BFNIS diagnosis as well as aspects of mutations in particular genes that are related to BFNIS and BFNS. In particular the reference teaches a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Relevant to the limitations of claims 1-4, the reference provides that there is a clinico-molecular correlation between mutations in the SCN2A gene and the BFNIS phenotype, where in two family based studies missense mutations in the SCN2A cosegregate with the BFNIS phenotype in affected relatives of probands in two pedigree analyses (p.851 – Abstract; Figure 1).

Relevant to claims 5 and 6, the reference teaches analyses that include an SSCA assay and a sequencing assay, thus providing an assay to test for the presence of an alteration and assay to identify the nature of the alteration (p. 851, left col.).

Relevant to claim 7, the reference provides that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Relevant to claim 8, the reference teaches testing for the presence of alterations in the SCN2A gene and the KCNQ2 and KCNQ3 genes (e.g. p.851, right col.), as well teaching a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.). The reference

further provides diagnostic parameters (e.g. age of seizure onset) for BFNIS, BFIS, and BFNS.

Relevant to claims 9 and 10, the reference teaches analyses that include an SSCA assay and a sequencing assay, thus providing an assay to test for the presence of an alteration and assay to identify the nature of the alteration (p. 851, left col.).

Relevant to claim 17, the reference provides that individuals were screened with single-strand conformation analysis (SSCA) (p.851 – left col.), which is an SSCP assay.

Relevant to claim 24, the reference teaches the sequencing of exons to identify the nature of detected alterations (p.852 – left col.).

The teachings of Heron et al do not provide diagnostic methods per se. However, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have to have used the express teachings of Heron et al, particularly regarding the specific times of onset of seizures BFNS, BFIS, and BFNIS, the teachings regarding the clinico-molecular correlation between SCNA2 mutations and BFNIS, and the teaching that BFNS is frequently caused by KCNQ2 and KCNQ3 mutations, to develop methods of diagnosing a particular phenotype from among BFNS, BFIS, and BFNIS where SCN2A mutations are indicative of BFNIS and KCNQ2 and/or KCNQ3 mutations are indicative of BFNS, as required by the claims. One would have been motivated to create such diagnostic methodologies as the skilled artisan would recognize that using molecular analysis of genes associated with the particular conditions would allow more accurate diagnosis of distinct phenotypes with similar symptoms.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the teachings of the prior art. Applicants' arguments (p.13-16 of the Remarks) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection.

Applicants have argued that there is no teaching of suggestion in the prior art to arrive at the instantly claimed diagnostic methods, and that the teachings of the cited prior art cannot be modified to arrive at the claimed methods without hindsight vision. Applicants have further argued that the cited prior art provides no reasonable expectation of success that modification of the methods of the prior art will arrive at a diagnostic method as claimed.

The Examiner maintains that the plain teachings of the prior art render obvious the claimed diagnostic methods. Where the prior art sates that the teachings of the prior art provide a "clinico-molecular correlation that defines a new benign familial epilepsy syndrome beginning in early infancy", and also that "benign familial neonatal-infantile seizures represents a new clinically recognisable autosomal dominant syndrome with an underlying molecular basis", the prior art demonstrates to the skilled artisan that SCN2A mutations, and certainly at least the particular mutations disclosed in Fig 2 of the reference, may be used to correlate an SCN2A mutation genotype with a BFNIS phenotype. While the data of the instant specification may provide for that analysis of more or different subject and thus expand upon the teachings of the prior art,

the teaching of the prior art are very clear that the molecular mutations are usable in determining the clinical status of a subject.

The rejection as set forth is **MAINTAINED.**

It is noted that Applicants have further traversed the remainder of the rejections under 35 USC 103 with the argument that the alleged deficiencies of Heron et al are not compensated for by the teachings of the additional cited prior art. Such arguments are not found to be persuasive as the Examiner has maintained that Heron et al does render obvious the methods as set forth above. As such the following rejections are maintained.

4. Claims 11, 12, 14-16, 18-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heron et al (2002) (citation #6 on the IDS of 5-25-2006), as applied to claims 1-10, 17 and 24 above, and further in view of Singh et al (2002) (US Patent 6,413,719).

Heron et al teaches several phenotypic parameters of BFIS, BFNS, and BFNIS diagnosis as well as aspects of mutations in particular genes that are related to BFNIS and BFNS. In particular the reference teaches a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Heron et al does not specifically provide for assays that include DNA hybridization (claim 11), probe hybridization to genomic DNA (claim 12), electrophoresis

(claim 14), analysis of exon length (claims 15 and 26); DNA amplification with allele specific oligonucleotides (claim 16), RNase protection (claim 18), DGGE (claim 19), enzymatic assays (claim 20), MutS assays (claim 21), and assays which examine protein electrophoretic mobility and immunoassays (claims 22 and 23). However, such assay methods in the analysis of mutations were well known in the art at the time the invention was made, and are taught by Sing et al for the analysis of mutations in the KCNQ2 and KCNQ3 genes as associated with BFNS.

Relevant to the rejected claims, Singh et al provides for assays that include DNA hybridization (e.g.: Fig 1, relevant to claim 11), probe hybridization to genomic DNA (e.g.: Fig 1; col.11 lns.35-40, relevant to claim 12), electrophoresis (e.g.: col.7 lns.55-65; col.8 lns.45-56, relevant to claim 14), DNA amplification with allele specific oligonucleotides (e.g.: col.11 lns.35-40, relevant to claim 16), RNase protection (e.g.: col. 9 lns.22-23, relevant to claim 18), DGGE (e.g.: col. 9 ln.22, relevant to claim 19), enzymatic assays (e.g.: col. 9 lns.22-23, relevant to claim 20), MutS assays (e.g. col.9 lns.3-5, relevant to claim 21), and assays which examine protein electrophoretic mobility and immunoassays (e.g.: col.11 lns.1-19, relevant to claims 22 and 23).

With regard to claims 15 and 26, Singh et al teaches amplification of exons using primers complementary to flanking introns (e.g.: Fig 7; col 15 – Example 17; Table 4). Sing et al further teaches that gene mutations may comprise deletions that shorten the resulting protein (col.7 lns.20-55; col.8 lns. 29-35). Further relevant to the limitations of claim 26, it is noted that both Heron et al and Singh et al teach sequence analysis of genes to identify mutations.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods disclosed in Singh et al for the analysis and detection of alterations of genes associated with BFNS and BFNIS, as required by the claimed methods. The skilled artisan would have been motivated to use the methods as disclosed in Singh et al as the skilled artisan would recognize that such methods would provide alternative means for the analysis of gene alterations.

With regard to claims 15 and 26, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the size of amplified SCN2A, KCNQ2 or KCNQ3 exons in a subject as compared known wild type exon lengths to detect exon alterations that are shorter in a subject exon and are thus indicative of a truncated encoded-protein. One would have been motivated to identify such alterations as both Heron et al and Singh et al indicate that loss of protein function may result in the pathological phenotype, where the skilled artisan would recognize, based on at least on the teachings of Singh et al, that gene deletion and protein truncation may result in loss of function.

5. Claims 13 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heron et al (2002) (citation #6 on the IDS of 5-25-2006), as applied to claims 1-10, 17 and 24 above, and further in view of Claes et al (2002) (US Patent 6,413,719).

Heron et al teaches several phenotypic parameters of BFIS, BFNS, and BFNIS diagnosis as well as aspects of mutations in particular genes that are related to BFNIS and BFNS. In particular the reference teaches a clinico-molecular correlation between

missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Heron et al does not specifically provide for assays using high performance liquid chromatography (claim 13), or the specific comparisons used in the SSCA assay (relevant to claim 25). However, such assay methods in the analysis of mutations were well known in the art at the time the invention was made, and are taught by Claes et al for the analysis of mutations in the genes as associated with epilepsy.

Relevant to claims 13 and 25, Claes et al teaches amplification of subject gene exons (Table 1) and analysis of amplicon properties using high performance liquid chromatography (p.1328 – Mutation detection and molecular-genetic analysis). The methods of Claes et al comprise detecting aberrant DHPLC patterns of amplicons, and sequence analysis of exons with aberrant patterns.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the mutation detection and analysis methods of Claes et al for the detection and analysis of SCN2A mutations associated with BFNIS as taught by Heron et al. In a combination of such methods it would be obvious to compare the DHPLC patterns of amplicons of subject exons with the patterns of the same exons from non-mutant genes, where Heron et al provides that mutations in the SCN2A gene, as compared to wild-type gene sequences, are causative of BFNIS. One would have been motivated to use the particular methodologies rendered obvious by Heron et al in view of Claes et al based on the teachings of Heron et al that SSCA

followed by sequence analysis is useful for mutation detection, and the successful application of the particular methodological techniques of Claes et al.

6. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heron et al (2002) (citation #6 on the IDS of 5-25-2006), as applied to claims 1-10, 17 and 24 above, and further in view of Smtih et al (1996).

Heron et al teaches several phenotypic parameters of BFIS, BFNS, and BFNIS diagnosis as well as aspects of mutations in particular genes that are related to BFNIS and BFNS. In particular the reference teaches a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Heron et al does not specifically provide for assays comprising hybridizing amplified exon fragments from a subject with exons from non-mutant SCN2A gene. However, such methods for mutation detection were well known in the art at the time the invention was made.

Smith et al teaches methods for mutation detection wherein heterogeneous nucleic acids are hybridized, and non-complementary nucleic acids that from heteroduplexes are identified (e.g. p.4375 – Detection of mutations in PCR-amplified gene fragments).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the mutation detection and analysis methods

of Smith et al for the detection and analysis of SCN2A mutations associated with BFNIS as taught by Heron et al. In a combination of such methods it would be obvious to hybridize amplicons of subject exons with the amplicons of the same exons from non-mutant SCN2A genes, where Heron et al provides that mutations in the SCN2A gene, as compared to wild-type gene sequences, are causative of BFNIS. One would have been motivated to use the particular methodologies rendered obvious by Heron et al in view of Smith et al based on the teachings of Heron et al that mutation detection followed by sequence analysis is useful for mutation detection, and the teachings of Smith et al that methods comprising the detection of heteroduplexes are generally applicable for mutation screens (p.4379 – left col.)..

Conclusion

7. No claim is allowed.

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

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/Stephen Kapushoc/
Primary Examiner, Art Unit 1634